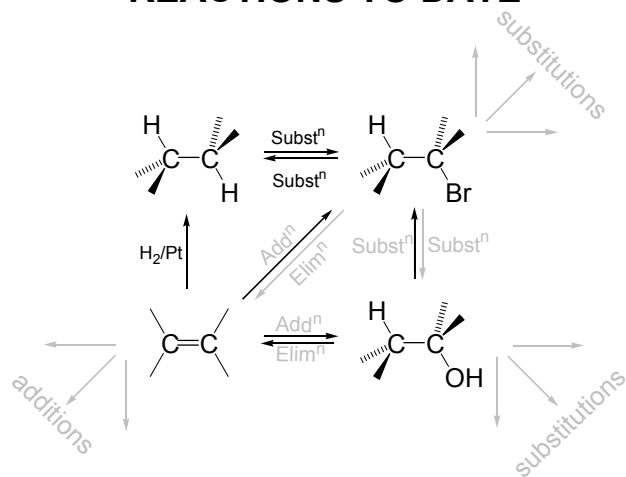


TOPIC 6. NUCLEOPHILIC SUBSTITUTIONS

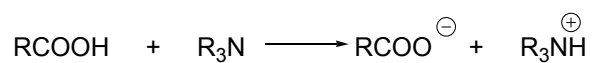
OBJECTIVES

1. Describe two pathways (mechanisms) to account for substitution at sp^3 carbons bearing an electronegative atom (leaving group)
2. Discuss the effect of starting material (substrate), leaving group, reagent (a nucleophile) and reaction conditions on the course of a reaction
3. Recognize functional group transformations and synthesis of new molecules in one step by substitution of an appropriate material
4. Explore the substitution chemistry of alcohols and ethers

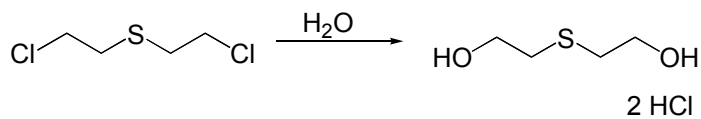
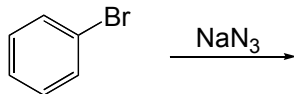
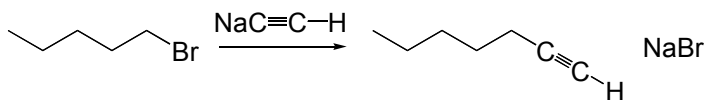
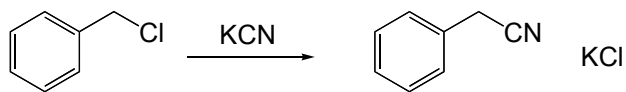
REACTIONS TO DATE

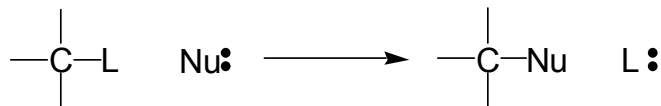


Acid-Base Chemistry



OVERVIEW: NUCLEOPHILIC SUBSTITUTIONS





We are only considering sp^3 (alkyl) substrates in this section. Molecules with leaving groups on sp^2 (e.g., vinyl, aryl) or sp (ethynyl) carbons do not react in fashion described in this section

Nucleophiles

Donate a pair of electrons: to an electrophile (lone pair or pi bond)

Neutral H_2O $\text{H}_2\text{C}=\text{CH}_2$

Anionic $\text{H}\ddot{\text{O}}:^{\ominus}$

Electrophiles

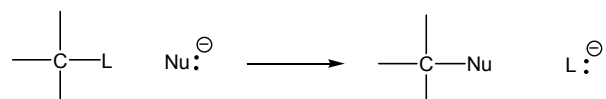
Receive a pair of electrons: from a nucleophile

Cationic $\begin{array}{c} | \\ \text{---C}^{\oplus} \\ | \end{array}$

Lacks an octet $\begin{array}{c} \text{Cl} \\ | \\ \text{Al} \\ / \quad \backslash \\ \text{Cl} \quad \text{Cl} \end{array}$

Polar, electrophilic $\begin{array}{c} | \\ \text{---C---X} \\ | \end{array}$

Effect of Leaving Groups on Electrophilicity



C-L bond must be polarizable

C-L bond must be relatively weak

L needs to be able to accommodate a pair of electrons

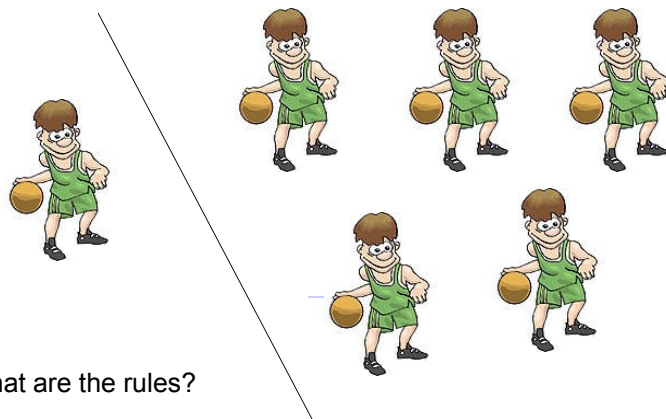
⇒ Good leaving groups are weak bases

Which of the following is the best leaving group in a nucleophilic substitution reaction?

- 1 H:^{\ominus}
- 2 $\text{H}_3\text{C:}^{\ominus}$
- 3 $\text{H}\ddot{\text{O}}:\text{}^{\ominus}$
- 4 $:\ddot{\text{Br}}:\text{}^{\ominus}$
- 5 $\text{H}_2\ddot{\text{N}}:\text{}^{\ominus}$

Substitution: What is the Mechanism?

substitute /'sêb-,stê,t(y)üt/ *vb*: to put in the place of another



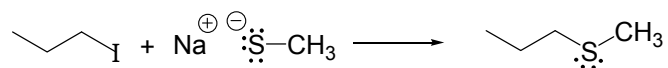
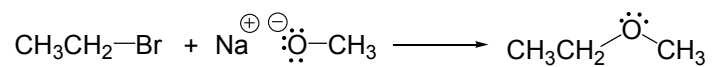
TWO CLASSES OF REACTION

Substitution reactions can be performed under different conditions which give rise to dramatically different outcomes. Nucleophilic substitution reactions can be classified as one of two types, based on these experimental observations.

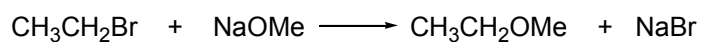
In order to develop predictive tools, we need to *understand* reasons *why* these observations are important. That is, we need to develop proposals for two different mechanisms which are consistent with the two sets of data and *which we can use to predict the outcome of other reactions*.

SUBSTITUTION AT 1° SUBSTRATES: BIMOLECULAR NUCLEOPHILIC SUBSTITUTION (S_N2)

Examples



Kinetics



[CH ₃ CH ₂ Br]	[NaOMe]	relative rate
0.01 M	0.01 M	1
0.02 M	0.01 M	2
<hr/> 0.01 M	<hr/> 0.02 M	<hr/> 2
0.02 M	0.02 M	4

Conclusion: Rate = $k[\text{R-L}][\text{Nu}]$

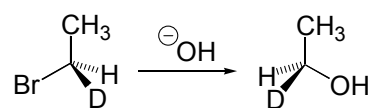
Slide 13

d1 d-laptop, 8/6/2007

Mechanism of Nucleophilic Substitution of 1° Alkyl Halides: The S_N2 Reaction

Chirality

Chiral R-L forms R-Nu with opposite stereochemistry (inversion of stereochemistry, "Walden Inversion")



Interpretation:

Nu:



Nucleophilicity

Basicity and nucleophilicity are not the same, but they are related phenomena

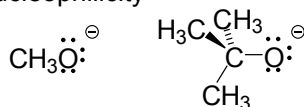
A negatively charged nucleophile is more reactive than its conjugate acid.



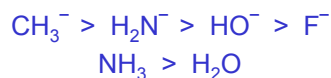
In a group of nucleophiles in which the nucleophilic atom is the same, nucleophilicity parallels trends in basicity.




Steric bulk hinders nucleophilicity



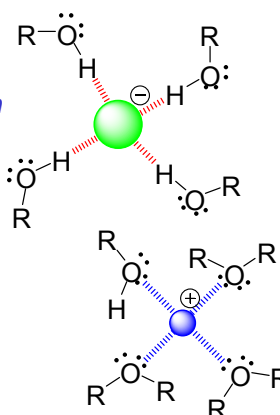
Across a row in the periodic table, nucleophilicity parallels trends in basicity.



Down a column in the periodic table, trends in nucleophilicity of anions depend on the choice of solvent.

polar protic	{	H ₂ O	
		CH ₃ CO ₂ H	
		MeOH	
		EtOH	
polar aprotic	{	(CH ₃) ₂ SO – DMSO	dimethyl sulfoxide
		CH ₃ CN – AN	acetonitrile
		(CH ₃) ₂ NCHO – DMF	<i>N,N</i> -dimethylformamide
		CH ₃ COCH ₃	acetone
		CH ₂ Cl ₂	methylene chloride
		 – THF	tetrahydrofuran
		Et ₂ O – “ ether ”	diethyl ether
non-polar	{	CH ₃ (CH ₂) ₄ CH ₃	
		benzene	

Protic solvents solvate the anions (nucleophiles) by H-bonding and cations (counterions). Small electronegative anions particularly are well solvated, lowering their nucleophilicity. *Trends in nucleophilicity in polar protic solvents increases going down a column of the periodic table*



Polar aprotic solvents cannot hydrogen bond to anions (but do solvate cations). *Trends in nucleophilicity in polar aprotic solvents parallels trends in basicity.*

Large neutral nucleophiles (H_2S , PR_3) are highly polarizable and can donate more electron density than smaller neutral nucleophiles.

Nucleophilicity of Anions

H								He
Li	Be	B	C	N	O	F		Ne
			CH_3^-	NH_2^-	OH^-	F^-		
Na	Mg	Al	Si	P	S	Cl		Ar
					SH^-	Cl^-		
K	Ca		Ga	Ge	As	Se	Br	Kr
						SeH^-	Br^-	
							I	
							I^-	

nucleophilicity \uparrow
 base strength \uparrow
 nucleophilicity in **APROTIC** solvents \uparrow
 nucleophilicity in **protic** solvents \downarrow

Relative Nucleophilicity (in MeOH)

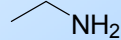
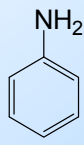
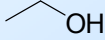
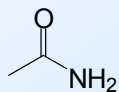
			Relative Nucleophilicity
Excellent Nucleophiles	CN ⁻	Cyanide	126,000
	HS ⁻	Thiolate	126,000
	I ⁻	Iodide	80,000
Good Nucleophiles	OH ⁻	Hydroxide	16,000
	Br ⁻	Bromide	10,000
	N ₃ ⁻	Azide	10,000
	NH ₃	Ammonia	8000
	NO ₂ ⁻	Nitrite	5000
Fair Nucleophiles	Cl ⁻	Chloride	1000
	CH ₃ COO ⁻	Acetate	630
	F ⁻	Fluoride	80
	CH ₃ OH	Methanol	1
	H ₂ O	Water	1

Nucleophilic relative strength is measured by relative rate in an S_N2 reaction (but depends on substrate, solvent type, etc.)

Which of the following is the best (most reactive) nucleophile in methanol?

- 1 H₂S
- 2 HO⁻
- 3 HS⁻
- 4 F⁻
- 5 CH₃Br

Which of the following is the best (most reactive) neutral nucleophile?



Leaving Group Ability

Rate: $-I > -Br > -Cl \gg -F$

C-L bond must be broken – weaker bonds are more polarizable, easier to break

Bond strengths (kcal/mole):

C-F	116
C-Cl	79
C-Br	66
C-I	52

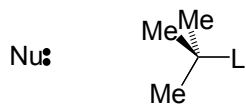
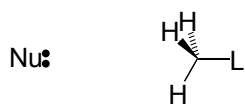
Overall: A good substrate for bimolecular nucleophilic substitution should have:

1. Weak C-L bond
2. Polarizable C-L bond (ease with which the electron distribution in the bond is distorted)
3. Leaving group that can accommodate a pair of electrons

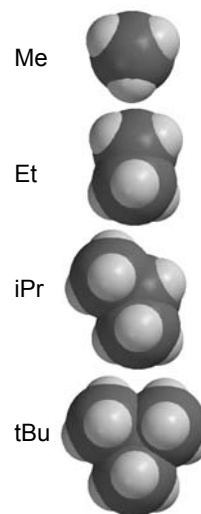
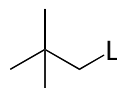
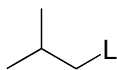
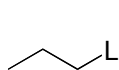
	Leaving group		pK _a of conjugate acid
Good Leaving Groups	I ⁻	Iodide	-10
	Br ⁻	Bromide	-9
	Cl ⁻	Chloride	-7
	RSO ₃ ⁻	Sulfonate	-6.5
	H ₂ O	Water	-1.7
Very Poor Leaving Groups	F ⁻	Fluoride	3.2
	HS ⁻	Thiolate	7
	⁻ CN	Cyanide	9.2
	HO ⁻	Hydroxide	15.7
	RO ⁻	Alkoxide	16-18
	H ⁻	Hydride	35
	⁻ NH ₂	Amino	38
	⁻ CH ₃	Methyl	48

Alkyl Substrates

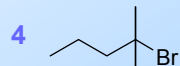
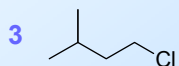
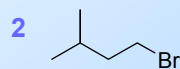
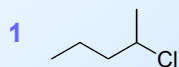
Rate: methyl > 1° > 2° (3° unreactive)



Adjacent alkyl groups also slow the reaction

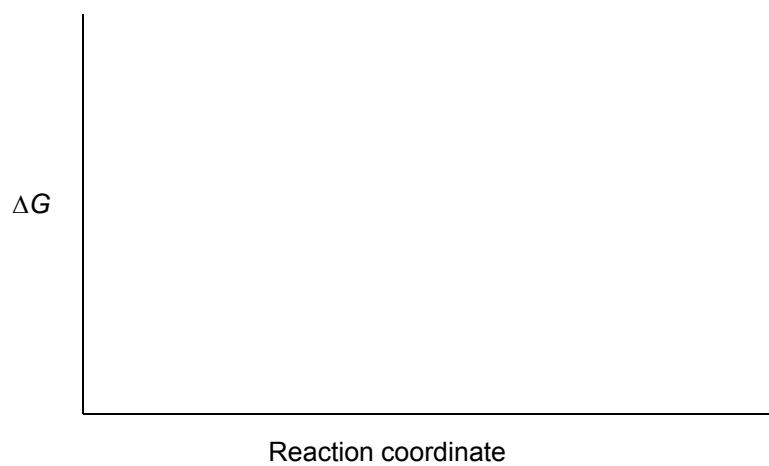


Which of the following undergoes the fastest S_N2 reaction with sodium cyanide?

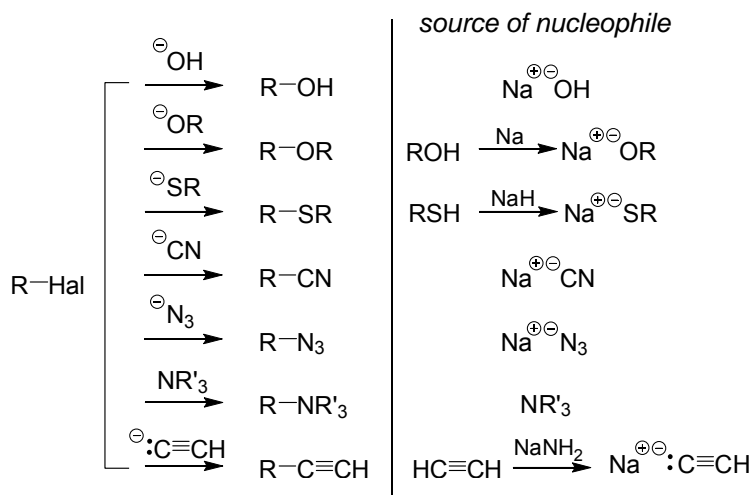


Energetics of One-Step (*i.e.*, concerted) Reaction

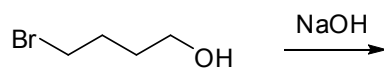
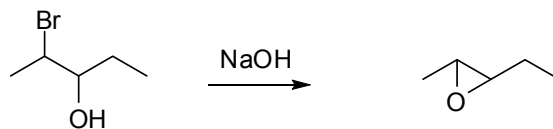
S_N2



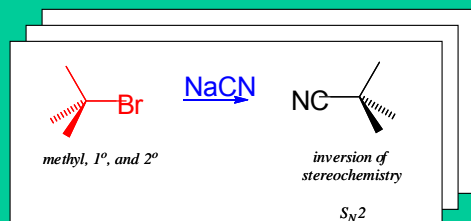
Practical Applications of S_N2 Reactions: Functional Group Transformations at 1° and 2° Carbons



Intramolecular S_N2 Reactions - Cyclizations



~ MAKE FLASHCARDS ~



front

back

Substrate + Reagent
(and conditions)

Substrate + Reagent
(and conditions)

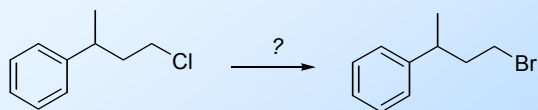
Substrate
and Product

Substrate
and Product

Reagent (and
conditions) and
Product

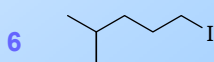
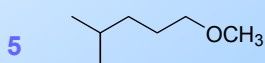
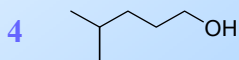
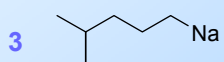
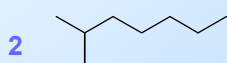
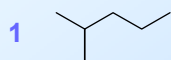
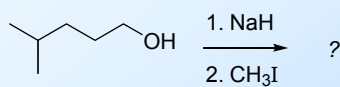
Reagent (and
conditions) and
Product

What is the reagent to perform the following transformation?

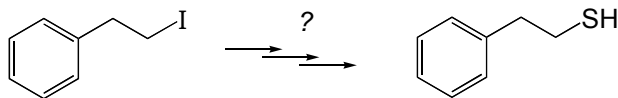


- 1 Br₂
- 2 HBr
- 3 NaBr
- 4 CH₃Br

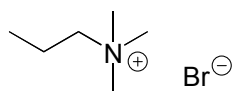
What is the product of the following reaction?



Problem: How would you prepare 2-phenylethanethiol from 1-iodo-2-phenylethane?



Problem: How would you make the following compound from 1-bromopropane and any other starting materials?

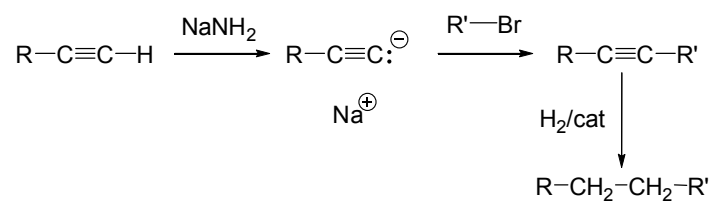


Problem: Which of the following would undergo the fastest reaction with 1-bromopropane in a polar protic solvent?

(a) Ph_3N or Ph_3P

(b) 1.0 M CH_3ONa or 2.0 M CH_3ONa

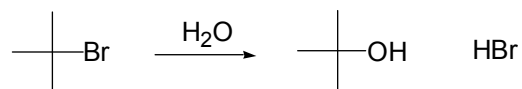
Synthesis of Alkynes and Alkanes: Alkylation of Acetylide Anions



R' must be 1°

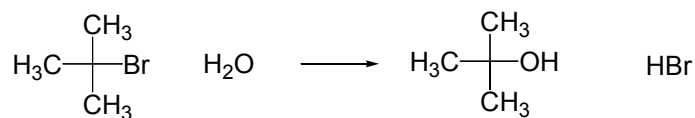
SUBSTITUTION AT 3° SUBSTRATES: UNIMOLECULAR NUCLEOPHILIC SUBSTITUTION (S_N1)

Example



Experimental observations of kinetics, chirality, substrate structure and effect of nucleophiles for this reaction are inconsistent with the S_N2 mechanism

Kinetics



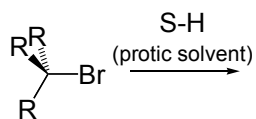
<u>[<i>t</i>-BuBr]</u>	<u>[H₂O]</u>	<u>relative rate</u>
0.01 M	0.01 M	1
0.02 M	0.01 M	2
0.01 M	0.02 M	1
0.02 M	0.02 M	2

Result: Rate = $k[\text{R-L}]$ independent of concentration of Nu

Mechanism of Nucleophilic Substitution of 3° Alkyl Halides: S_N1

Practical Applications of S_N1 Reactions: Solvolysis

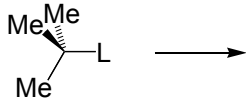
The only practical S_N1 reactions are *solvolyses*, reactions in which the solvent also acts as the nucleophile. These reactions arise because solvents which are polar enough to facilitate dissociation of the substrate are also nucleophilic



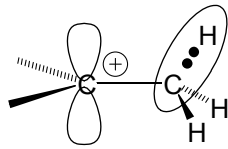
Substrates

Rate: $3^\circ > 2^\circ$ (1° , methyl not reactive)

Interpretation:



Stability of Carbocations

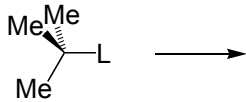


Carbocation	Relative Energy (kcal/mol)
Methyl	0
Ethyl	-37
<i>i</i> -Propyl	-65
<i>t</i> -Butyl	-83

- More substituted carbocation stabilized by hyperconjugation

Effect of Leaving Group

Rate: $-I > -Br > -Cl$ (F: unreactive)



C-L bond must be broken – weaker, polarizable bonds are easier to break

Bond strength: $C-F > C-Cl > C-Br > C-I$

Overall: A good substrate for unimolecular nucleophilic substitution should have:

1. Weak C-L bond
2. Polarizable C-L bond (ease with which the electron distribution in the bond is distorted)
3. Leaving group which can accommodate a pair of electrons

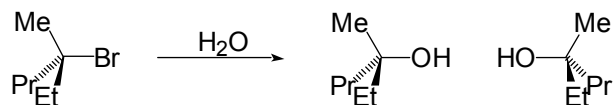
Effect of Nucleophile/Solvent

Rate independent of *concentration* of nucleophile (solvent)

Rate depends on *polarity* of solvent

Chirality

A single enantiomer of substrate with the leaving group on the stereogenic center reacts to give product that consists of a mixture of both enantiomers.

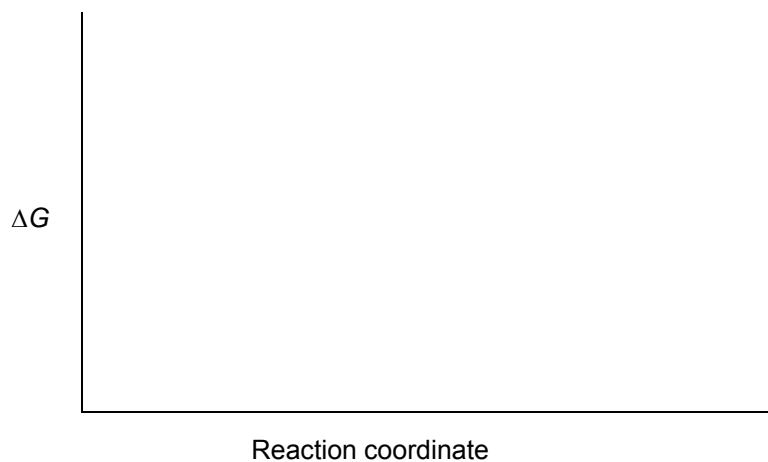


Which of the following would undergo the most rapid acidolysis (e.g., substitution with acetic acid)?

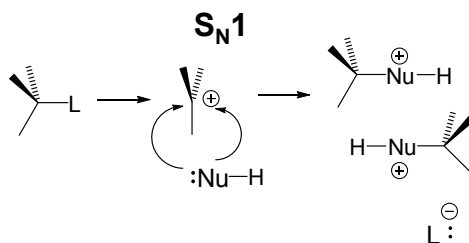
- 1 (CH₃)₃CBr
- 2 (CH₃)₃CF
- 3 CH₃Cl
- 4 (CH₃)₃CCl
- 5 CH₃CH₂Br

Energetics of a Two-Step Reaction

S_N1



SUMMARY: FACTORS EFFECTING S_N1 AND S_N2 REACTIONS



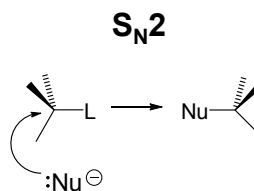
Dissociation-Nucleophilic addition-Deprotonation

Substrate: $3^\circ > 2^\circ \gg 1^\circ$ or methyl
- Stability of carbocation intermediate

Rate = k [substrate]
- independent of [nucleophile]
- rate depends on solvent polarity

Chirality
- racemization

Generally only useful for solvolyses
(reactions with H_2O , ROH , RCO_2H)



One-step (concerted) mechanism

Substrate: Methyl $> 1^\circ > 2^\circ \gg 3^\circ$
- Steric bulk hinders attack of Nu

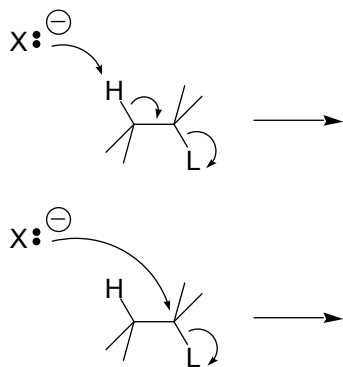
Rate = k [substrate] [nucleophile]

Chirality
- Inversion

Often performed in polar aprotic solvents, e.g., DMF (Me_2NCHO), DMSO (Me_2SO) to dissolve substrate and ionic reagent, and increase reaction rate

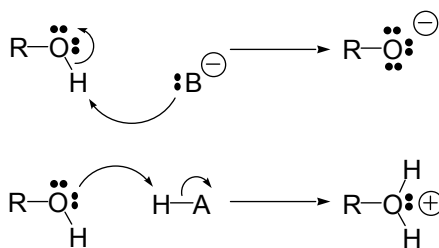
A Limitation to Reactions of Alkyl Halides with Nucleophiles

Elimination competes with substitution if the nucleophile is too basic or if the electrophile is too crowded (we will explore this further in Topic 7)



SUBSTITUTION REACTIONS OF ALCOHOLS

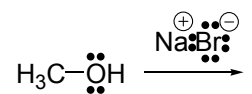
Alcohols as Acids and Bases



Alcohols are weak acids and weak bases. Acid-base chemistry is important in activating the electrophilic and nucleophilic character of alcohols, respectively.

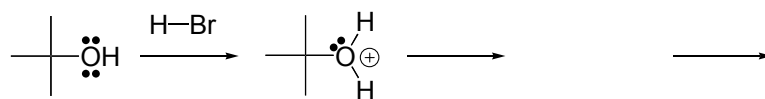
Conversion Of Alcohols To Alkyl Halides

Alcohols do not react with sodium halides to give alkyl halides!

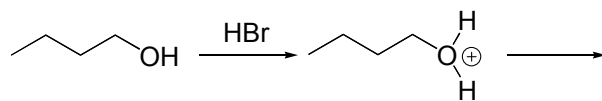


Alcohol + H-Hal

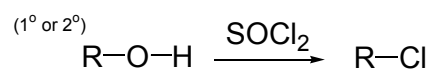
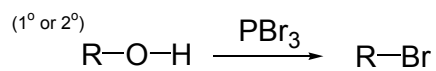
3° Alcohols: S_N1



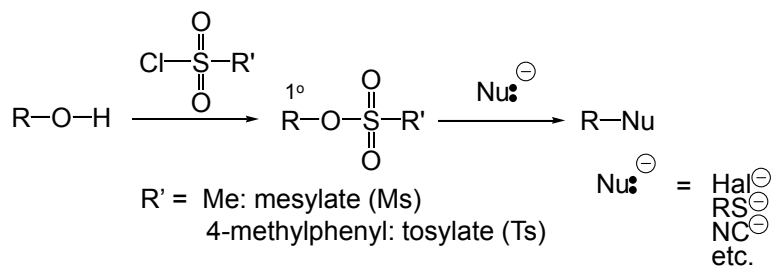
1° Alcohols: S_N2



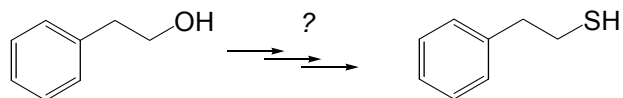
Other reagents



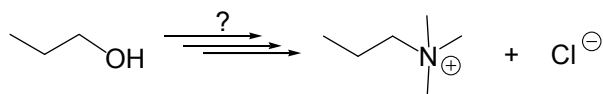
MESYLATES AND TOSYLATES IN S_N2 REACTIONS



Problem: How would you prepare 2-phenylethanethiol from 2-phenyl-1-ethanol?



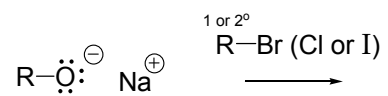
Problem: How would you make the following product from 1-propanol and any other starting materials?



SYNTHESIS OF ETHERS

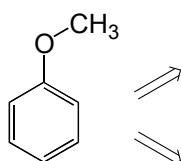
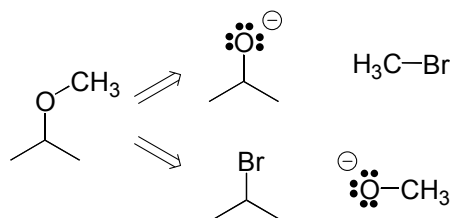
Synthesis of Ethers: Williamson Ether Synthesis

Overall Reaction and Mechanism

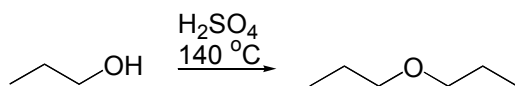


Designing Williamson Ether Syntheses

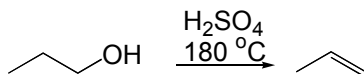
You could suggest making either C-O bond of the ether.



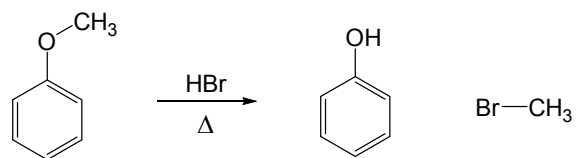
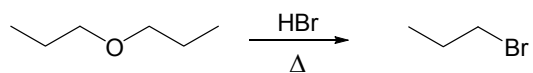
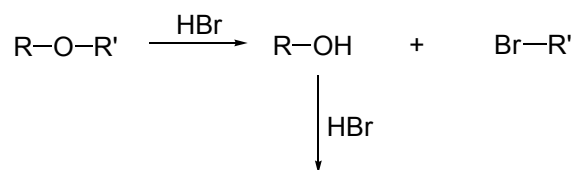
Synthesis of Symmetrical Ethers: Dehydration of Alcohols



At higher temperature a competing reaction predominates (elimination of water to form an alkene, see Topic 7)



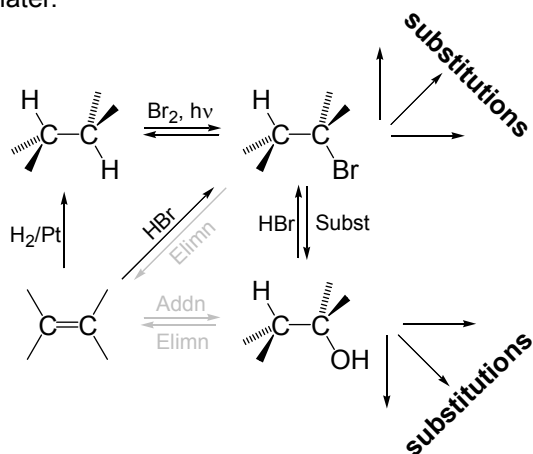
Reaction of Ethers: Acid-catalyzed Hydrolysis



SUBSTITUTIONS IN SYNTHESIS

You should prepare a chart of all of the types of reactions that have been covered so far...

....we'll add more later.

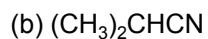
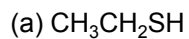


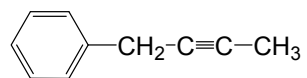
ONE-STEP SYNTHESSES

It is important to recognize transformations which can be performed in a single step. Use the thought process:

- *What can the product can be made from?*
PRODUCT \Rightarrow STARTING MATERIAL
- The synthesis itself is
STARTING MATERIAL \rightarrow PRODUCT

Problem: How would you prepare the following from appropriate alkyl chlorides?





from starting materials with 7 or fewer carbon atoms

Problem: How can you prepare the following two compounds from the appropriate alkyl bromide?

(a) Methyl phenyl ether, Me-O-Ph

(b) (S)-2-Pentanol, CH₃CH(OH)CH₂CH₂CH₃

Problem: How could you perform the following synthesis? [An introduction to designing multi-step syntheses]



TOPIC 6

Types of Questions

- Recognize factors which influence the mechanism of nucleophilic substitutions (SN1 versus SN2)
- Predict outcomes of substitution reactions